Dr. Puttagunta is a Fellow in the Division of Endocrinology and Dr. Toth is Associate Professor in the Division of Endocrinology and Director of Postgraduate Education, Department of Medicine, University of Alberta, Edmonton, Alta.

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Insulin lispro (Humalog), the first marketed insulin analogue: indications, contraindications and need for further study

Anuradha L. Puttagunta, MB, BS; Ellen L. Toth, MD

Abstract

Objective: To review the available literature on the new insulin analogue insulin lispro and provide information on its efficacy, indications for use and contraindications.

Data sources: MEDLINE searches were made for articles published from 1966 to 1996 using the indexing terms "lispro," "Humalog" and "insulin analogs."

Study selection: About 30 studies and review articles were selected based on their relevance to the stated objective. These were critically appraised for the purpose of writing the review article so that it would be relevant to general practitioners, internists and nurse educators.

Data synthesis: The therapeutic challenge when treating diabetic patients is to bring the blood glucose level into as normal a range as possible, with minimal hypoglycemia and hyperinsulinemia. Insulin lispro has a much faster, higher and shorter-lasting peak serum insulin level than regular human insulin, thus mimicking physiologic secretion of insulin more closely. As a result, there is improvement in postprandial blood glucose levels and decreased episodes of hypoglycemia, with no change in the hemoglobin A_{1c} ($HgbA_{1c}$) level. The ability to inject insulin lispro immediately before the meal allows greater flexibility of lifestyle. Compared with regular insulin, insulin lispro is associated with a lower risk of hypoglycemia with exercise several hours after a meal. It is therefore most useful for the motivated, compliant diabetic patient who would like to achieve a better hypoglycemia–$HgbA_{1c}$ ratio as well as for patients desiring further flexibility with premeal insulin injections. Use of insulin lispro has been shown to improve $HgbA_{1c}$ levels in patients using insulin pumps. It is well tolerated, and therapy is often continued after studies are completed. Further study is needed to establish optimal basal regimens.

Résumé

Objectif : Revoir les publications disponibles sur un nouvel analogue de l'insuline, l'insuline lispro, et fournir des renseignements sur son efficacité, sur les indications relatives à son utilisation et sur les contre-indications.

Sources de données : Rechercher dans MEDLINE des articles publiés entre 1966 et 1996 en utilisant les termes d'indexation «lispro», «Humalog» et «insulin analogs».

Sélection d'études : On a choisi une trentaine d'études et d'articles de critique en fonction de leur pertinence à l'objectif énoncé. On a procédé à une évaluation critique afin de rédiger l'article de critique de façon à ce qu'il soit pertinent pour les omnipraticiens, les internistes et les éducateurs en soins infirmiers.

Synthèse des données : Lorsque l'on traite des patients diabétiques, le défi thérapeutique consiste à normaliser le plus possible la glycémie en réduisant au minimum l'hypoglycémie et l'hyperinsulinémie. L'insuline lispro a un taux d'insuline sérique de pointe plus rapide, plus élevé et de moindre durée que l'insuline humaine ordinaire et imite ainsi de plus près la sécrétion physiologique de l'insuline. Il en découle une amélioration de la glycémie postprandiale et une réduction du nombre des épisodes d'hypoglycémie sans changement du taux

d'hémoglobine A_{1c} (HgbA$_{1c}$). La possibilité d'injecter l'insuline lispro immédiatement avant le repas assouplit considérablement le style de vie. Comparativement à l'insuline ordinaire, l'insuline lispro entraîne un plus faible risque d'hypoglycémie causée par l'exercice plusieurs heures après un repas. Elle est donc des plus utiles pour les patients diabétiques qui suivent leur traitement, sont motivés et aimeraient parvenir à un meilleur ratio hypoglycémie–HgbA$_{1c}$, ainsi que pour les patients qui souhaitent avoir plus de flexibilité quant aux injections d'insuline avant le repas. Il a été démontré que l'utilisation de l'insuline lispro améliore les taux de HgbA$_{1c}$ chez les patients qui utilisent des pompes à insuline. Elle est bien tolérée et l'on continue souvent le traitement une fois les études terminées. D'autres études s'imposent si l'on veut établir des régimes de base optimaux.

The discovery of insulin, in 1922, allowed patients with insulin-dependent diabetes mellitus (IDDM) to survive into adulthood. This was the start of a series of improvements in the treatment of diabetes that continues to the present day. The next important step was the development of the modified insulins, including isophane insulin suspension (neutral protamine Hagedorn [NPH]) in the 1940s and insulin lente in the 1950s.[1] In the 1970s the purity of insulin was improved through advances in protein chromatography technology. In the 1980s recombinant DNA technology allowed the manufacture of human insulin on a commercial scale.[2] All these improvements led to decreased immunologic complications, such as allergy, lipoatrophy and insulin resistance. However, replication of the natural patterns of insulin secretion remained elusive, making the management of IDDM a continued challenge.

Since the results of the Diabetes Control and Complications Trial were published,[3] the benefits of good glycemic control have been clearly established. One strategy to achieve good glycemic control and attempt to mimic physiologic secretion of insulin has been to use regular human insulin at mealtimes to control postprandial blood glucose excursions ("boluses") while providing "basal" insulin action with the longer-acting insulin formulations. However, absorption of regular human insulin from the subcutaneous tissue is limited by its existence as hexameric complexes that have to dissociate into dimers and monomers before passing the endothelial cell barrier and entering the bloodstream.[4] As a result, the rate of increase in plasma insulin levels is slower, and the peak is smaller than physiologic insulin secretion in healthy subjects. Postpeak plasma insulin levels are also higher than physiologic levels.[5] To achieve optimal results, therefore, patients should administer regular human insulin 20 to 45 minutes before a meal. Also, because insulin levels remain elevated for more than 2 to 3 hours, patients need to eat snacks to avoid late hypoglycemia before the next meal.[6]

To circumvent these problems, various insulin analogues have been manufactured synthetically. The first to be marketed in Canada and elsewhere is insulin lispro (Humalog), which has an inversion of the amino acids proline and lysine at positions 28 and 29 on the β chain of the human insulin molecule.[7] This modification causes a change in the tendency to self-aggregate, such that when injected, insulin lispro disassociates faster (from itself) and therefore has a faster onset and end time of action.[8] The onset of action is within 15 minutes, and the peak action is at 1 to 2 hours, as opposed to 2 to 4 hours with conventional insulin.[9,10]

The purpose of this review is to provide information to general practitioners, internists and nurse educators on the efficacy, risks and benefits of insulin lispro based on the available literature so that decisions about its use can be made objectively. To this purpose, we searched MEDLINE for articles published from 1966 to 1996 using the terms "lispro," "Humalog" and "insulin analogs." Most studies were randomized with parallel or crossover design and were open label. We chose the most informative and relevant references according to their level of evidence and their relevance to the purpose of the review.

Benefits

To date, insulin lispro has been used in clinical trials involving over 10 000 subjects worldwide. The first studies, in healthy volunteers, showed a much faster, higher and shorter-lasting peak serum insulin level compared with regular insulin[11] (Fig. 1). The action of insulin lispro lasts only 3 to 4 hours, compared with up to 6 hours for conventional insulin.

A crossover study involving 1008 patients with IDDM over 3 months showed higher postprandial glucose concentrations and reduced glucose excursions, with reduced rates of hypoglycemia, among patients using insulin lispro than among those using regular insulin.[12] This effect on postprandial glycemia was also noted in patients with non-insulin-dependent diabetes.[13] These findings were confirmed in several other studies, all of which were randomized controlled trials.[14–21] Unfortunately, most of the

trials were of short duration (less than 1 year) and were limited by the fact that they could not be blinded, as insulin lispro had to be injected immediately before a meal and regular insulin half an hour before a meal. A double-blinded study, however, showed similar results but was limited by the small number of subjects and short duration (3 months).[22] The results of the various studies comparing insulin lispro with regular insulin are summarized in Table 1.

In patients with IDDM of short duration with residual pancreatic β-cell function, insulin lispro controlled postprandial plasma glucose concentration better than regular insulin.[25] Insulin lispro provided better postprandial glycemia in patients with IDDM following a challenge with a carbohydrate-rich meal (pizza, cola and tiramisu) (Fig. 2).[26] In 30 patients with IDDM who were using insulin pumps, insulin lispro improved hemoglobin A_{1c} ($HgbA_{1c}$) levels without increasing the risk of hypoglycemia over 3 months.[27]

Significantly fewer hypoglycemic episodes were seen with insulin lispro than with regular insulin at 6 months in 39 young people with IDDM randomly assigned to one of the 2 groups (16.8 [standard error of the mean [SEM] 3.9] episodes per patient v. 4.7 [SEM 1.4] episodes per patient).[19] Pfutzner and colleagues[23] noted a decrease in hypoglycemic episodes (9.6 [SEM 0.72] v. 8.57 [SEM 0.7]) in 107 patients with IDDM randomly allocated to receive regular insulin or insulin lispro; there was no difference between the groups in $HgbA_{1c}$ level.

Pfutzner and colleagues[23] also administered a quality-of-life questionnaire to their patients and found higher satisfaction with treatment among those in the insulin lispro group. Most of the patients elected to continue using insulin lispro, stating convenience and flexibility as its biggest advantages.

Tuominen and associates[28] studied 10 patients with IDDM to examine the effect of insulin lispro on exercise-induced hypoglycemia. When exercise was performed 40 minutes after breakfast, the degree of exercise-induced hypoglycemia was 2.2 times greater with insulin lispro than with regular insulin. When exercise was performed 180 minutes after breakfast, the fall in plasma glucose was 46% less with insulin lispro than with regular insulin.
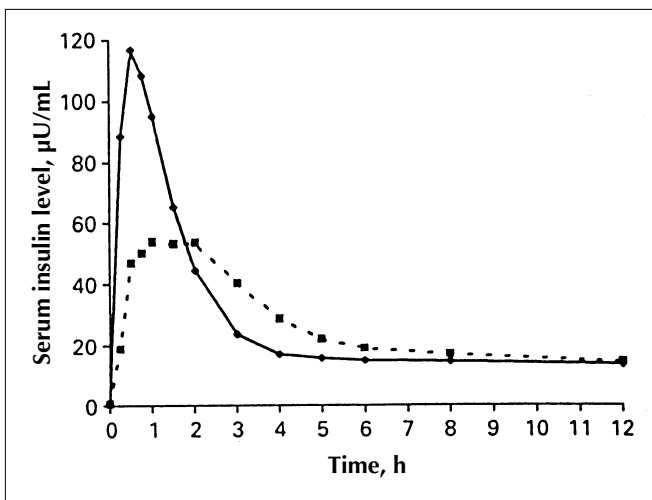

Fig. 1: Effects of subcutaneous administration of insulin lispro (solid line) and regular human insulin (dashed line) on serum insulin levels. (Adapted, with permission, from Howey et al.[7] © American Diabetes Association.)

Table 1: Studies comparing insulin lispro and regular insulin given in regimens involving multiple daily doses among patients with diabetes mellitus*

Study	No. of patients, type of diabetes	Study design	Duration of treatment	% difference in hemoglobin A_{1c} level	Difference in frequency of hypoglycemia, %	Difference in 2-h postprandial increase in glucose, mmol/L	Difference in fasting glucose levels, mmol/L
Anderson et al[12]	1008, IDDM	Crossover	3 mo	None	−12 ($p = 0.001$)	−2.0 ($p < 0.001$)	NA
Martin et al[14]	78, IDDM 28, NIDDM	Crossover	3 mo	None −0.3	−3‡	−2.6 −2.4	NA
Vignati et al[15]	336, IDDM 295, NIDDM	Parallel	1 yr	−0.2 ($p = 0.17$)	None	−1.1 ($p = 0.007$)	NA
Vignati et al[16]†	167, IDDM	Parallel	1 yr	−0.2 ($p = 0.03$)	None	−2.8 ($p = 0.001$)	+0.4 ($p = 0.50$)
Anderson et al[17]†	145, NIDDM	Parallel	1 yr	−0.2 ($p = 0.69$)	−16 ($p = 0.51$)	−1.4 ($p = 0.02$)	+0.3 ($p = 0.53$)
Brunelle et al[18]	722, NIDDM	Crossover	3 mo	None	−4 ($p = 0.31$)	−1.6 ($p < 0.001$)	+0.5 ($p = 0.002$)
Garg et al[19]	37, IDDM	Parallel	1 yr	+0.2	None	−4.0 ($p < 0.05$)	−0.1
Schmitt et al[21]	199, IDDM	Crossover	3 mo	None	−4	−1.8 ($p < 0.001$)	+0.4 ($p = 0.08$)
Rowe et al[22]	93§	Blinded, crossover	3 mo	None	None	−1.8 (NA)	+0.7 ($p = 0.02$)
Pfutzner et al[23]	104, IDDM	Crossover	3 mo	None	−11 ($p = 0.008$)	−1.7 ($p < 0.001$)	NA

*All differences are the differences between treatment with insulin lispro and treatment with regular insulin. IDDM = insulin-dependent diabetes mellitus, NIDDM = non-insulin-dependent diabetes mellitus, NA = not available.
†Data from this study were included in the overall analysis in Vignati et al.[15]
‡This value refers to both the patients with IDDM and those with NIDDM.
§The type of diabetes was not clearly specified.
Adapted from Holleman et al,[24] with permission from the publisher. © 1997 Massachusetts Medical Society. All rights reserved.

Risks

Hypoglycemia will appear rapidly if insulin lispro is injected and the meal is delayed or not taken. Hypoglycemia can occur early after meals or even during meals. This may be particularly problematic in children, older people or those in institutions or while dining out (i.e., in any circumstance in which the beginning and end of the meal cannot be predicted accurately). However, this can be circumvented by giving insulin lispro during or immediately after the meal. Patients with unreliable eating or absorption patterns, such as those with diabetic gastroparesis, would also be at risk for hypoglycemia. Hypoglycemia can also occur during exercise early after a meal (within 1 hour).

A study involving 8 diabetic subjects showed that the symptom responses to hypoglycemia induced by subcutaneous injection of insulin lispro and of regular insulin were no different.[29] No significant difference in insulin-specific antibody binding values were seen between regular insulin and insulin lispro.[30]

All experimental data to date indicate no risk of carcinogenic effects or other long-term side effects. However, a competitive product was in phase III trials when it was withdrawn from the market because of the development of mammary carcinoma in rats.

There are no data on the safety of insulin lispro in pregnancy in humans. Studies are under way involving patients with gestational diabetes but not those with IDDM. This raises the issue of use in women of childbearing age and the need to warn such patients of a possible risk. In animal studies insulin lispro has not been found to cross the placenta in significant amounts than regular insulin.

Indications

For most patients with diabetes good glycemic control should be the aim of the treatment strategy. The exact regimen to be used will be determined by several factors, including the patient's motivation, health beliefs, potential for self-management, general health status and social support.

Insulin lispro would be most beneficial for the motivated, compliant patient with IDDM who would be willing to monitor glycemia before meals in order to make dosage adjustments. Its safety profile appears excellent, and it is not more immunogenic than human insulin. Its use would be equally justified in motivated patients with non-insulin-dependent diabetes. It may be helpful in avoiding nocturnal hypoglycemia if supper is late. It is also more useful than regular insulin when dining out since it can be injected after the meal arrives. Particularly useful indications are listed in Table 2. Of note, patients must be able to afford insulin lispro, since in Canada it costs roughly twice as much as regular insulin and is not uniformly covered by provincial drug plans.

Available studies indicate that the most common regimen is multiple daily doses of insulin lispro, with NPH
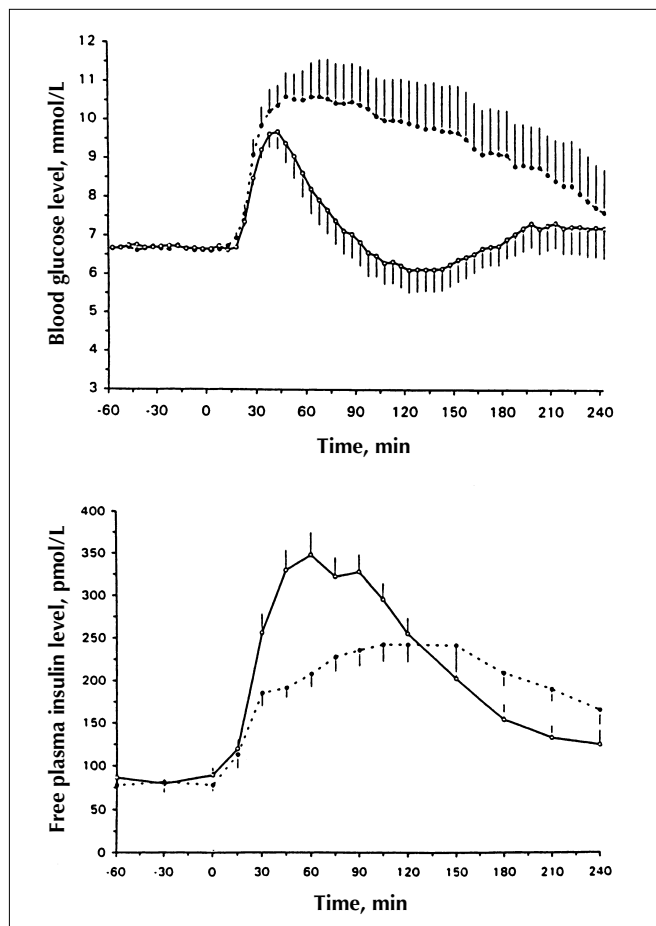

Fig. 2: Effects of subcutaneous injection of insulin lispro (solid lines) and regular human insulin (dotted lines) on blood glucose excursions (top) and free plasma insulin levels (bottom) of 10 patients with insulin-dependent diabetes mellitus after consumption of a carbohydrate-rich meal. Meal and injection given at 0 min. Error bars represent standard error of the mean. (Adapted, with permission, from Heinemann et al.[26] © John Wiley & Sons Limited.)

Table 2: Particularly useful indications for treatment with insulin lispro

Patients who need multiple injections who, despite advice, give injections immediately before meals

Patients with significant hypoglycemia at times of peak action of regular insulin

Patients with a high carbohydrate intake at meals

Patients with IDDM or NIDDM who are starting insulin therapy for whom insulin lispro would be preferable owing to flexibility or lifestyle issues

Motivated patients who are committed to routine blood glucose monitoring who desire to optimize glycemic control

given in the evening or at bedtime. However, a second dose of NPH may be necessary in the morning to avoid hyperglycemia in the late afternoon and evening. While switching over from regular insulin to insulin lispro, the first dose of the latter should be 5%–10% lower than the dose of regular insulin, but adjustments should subsequently be made, as determined by frequent monitoring of the blood glucose level. Insulin lispro could be combined with regular insulin if its postprandial effect is found to be too fast or excessive.

Contraindications

In the United States insulin lispro is not approved for use in children under 12 years of age, whereas in Canada there is no such limitation in the product monograph. Data from studies of insulin lispro in young children are being analysed. Insulin lispro has been given to young children before and after meals (given the unpredictability of their finishing a meal). It has been used in trials in adolescents, with similar trends to those in trials in adults.[19]

Further questions

Several questions regarding the use of insulin lispro remain unanswered. There seems to be a tendency for higher fasting and preprandial blood glucose levels with this analogue. No differences have been found between intermediate- and long-acting insulins (NPH and ultralente) as the basal components of the regimen.[12] The higher fasting and preprandial glucose levels may have resulted from the fact that these studies were performed without strict criteria for intensive diabetes management; rather, they had the aim of proving that insulin lispro was efficacious in "average" diabetic patients. This may also be the reason why differences in the HgbA$_{1c}$ level were not achieved. We suggest that studies involving tightly controlled and highly motivated patients may show differences in the HgbA$_{1c}$ level, as in the study involving insulin pump users.[27] These subjects should also be studied while using different basal insulins, both those currently available and those being developed (e.g., neutral protamine lispro).[24,31]

Other issues that need to be investigated in patients requiring intensive diabetes management are the role of snacks and the best time for blood glucose monitoring by the patient for dosage adjustment: before meals, after meals or some combination thereof. In patients unwilling or unable to carry out intensive diabetes management, the effect of mixing insulin lispro with intermediate- and long-acting insulins needs to be better understood, and studies are under way on premixtures, which are well accepted by patients.

Conclusion

The marketing of insulin lispro marks a new era in the use of insulin therapy in patients with diabetes. Further studies will probably make this an increasingly complex topic. Periodic updates will be necessary as physician specialists and diabetes educators continue to develop guidelines on this and other new insulin analogues that will almost certainly become available over the next decade. It is hoped that the increasingly sophisticated therapeutic arsenal will result in improved quality and quantity of life for all patients with diabetes.

The authors have no proprietary interest in any of the products mentioned in this article.

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Reprint requests to: *Dr. Ellen L. Toth, Division of Endocrinology, 362C Clinical Wing, Heritage Medical Research Centre, University of Alberta, Edmonton AB T6G 2S2; fax 403 492-6702; Ellen.Toth@Ualberta.Ca*

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